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Research report

Acute iboga alkaloid effects on extracellular serotonin (5-HT) levels in nucleus accumbens and striatum in rats

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Abstract

The iboga alkaloid, ibogaine, its metabolite, noribogaine, and the congener, 18-methoxycoronaridine (18-MC) have all been claimed to have anti-addictive properties in animal models, but the mechanisms underlying these effects are unclear. Ibogaine and noribogaine were shown to have affinity for the serotonin transporter, and inhibition of serotonin reuptake has been proposed to be involved in their anti-addictive actions. It is not known yet if 18-MC also has this property. In vivo microdialysis and HPLC (microbore) were used to determine acute changes in extracellular serotonin levels in nucleus accumbens (NAC) and striatum (STR) after both i.p. (40 mg/kg for all drugs) and i.v. (1–10 mg/kg for ibogaine and noribogaine) drug administration in awake freely moving female Sprague–Dawley rats (250–275 g). After i.p. administration, ibogaine, noribogaine and 18-MC had very different effects on extracellular serotonin levels in both NAC and STR: ibogaine elicited large increases (up to 25-fold in NAC and 10-fold in STR), noribogaine produced moderate increases (up to 8-fold in NAC and 5-fold in STR), and 18-MC had no effect in either brain region. These and other data suggest that (1) the serotonergic system may not be an essential factor in the anti-addictive actions of these drugs; (2) ibogaine (or an unidentified metabolite) may release serotonin as well as inhibit its reuptake; (3) stimulation of the ascending serotonergic system may mediate ibogaine's hallucinogenic effect; and (4) 18-MC probably has no affinity for the serotonin transporter, and is unlikely to be a hallucinogen. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Ibogaine; Noribogaine; 18-Methoxycoronaridine; Serotonin; In vivo microdialysis; Nucleus accumbens; Striatum; Rat

1. Introduction

Ibogaine is a naturally occurring alkaloid found in the root bark of a Central-West African shrub, *Tabernanthe iboga*. The history of its use by humans, as a stimulant at low doses and as a hallucinogen at high doses, can be traced back to the mid-nineteenth century; however, it did not gain much interest among researchers until the late 1980s, when a series of anecdotal observations appeared concerning its effectiveness in interrupting addiction to 'narcotics' (morphine and heroin), cocaine, amphetamine, alcohol and nicotine [29–33]. Amazingly, some patients seemed to remain free from drug dependence for two or more years after a single treatment [34]. In animal models, ibogaine was shown to dose-dependently attenuate the morphine withdrawal syndrome [cf. Ref. [15]] and decrease

self-administration of morphine [14,16], cocaine [6,14] and alcohol [49] for days to weeks, providing more evidence of its potential in treating addiction.

Unfortunately, ibogaine also exhibits neurotoxic effects that have limited its potential for use in humans. At high doses (100 mg/kg), in rats, it causes degeneration of Purkinje cells in the cerebellar vermis [41]. However, at behaviorally active doses (40 mg/kg, i.p.), in rats, ibogaine did not show neurotoxic effects [40], and this encouraged the development of synthetic derivatives that might further dissociate the anti-addictive and neurotoxic properties. One newly synthesized congener, 18-methoxycoronaridine (18-MC), is showing such potential. In animal models, it has been shown to decrease morphine and cocaine self-administration [13] and to reduce alcohol intake [50], but in neurotoxicity studies [13] it had no effect, even at high doses.

Another promising drug is ibogaine's metabolite, noribogaine, which was also demonstrated to decrease mor-

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phine, cocaine and alcohol self-administration in rats [12,48]. Because it was found to be present in plasma for a longer time than ibogaine, it has been postulated to mediate the long-term anti-addictive effect of ibogaine [12,37]. No neurotoxicity study of noribogaine has been reported.

Studies of the mechanisms of actions of ibogaine have implicated possible roles of κ [7,46] opioid receptors (probably agonist), sigma receptors (probably agonist) [35], NMDA receptors (probably antagonist) [38,47], serotonin transporters (probably inhibitor) [37], and nicotinic receptors (probably antagonist) [2]. In *in vivo* microdialysis studies, all three drugs have been shown to decrease dopamine levels in the nucleus accumbens (NAC) [12,13,36]. However, little information is known about their effects on other neurotransmitters, such as serotonin (5-HT). There is some evidence indicating a possible role of the serotonergic system in the actions of ibogaine and noribogaine: (1) ibogaine, noribogaine and serotonin all have the indole ring in their structures (Fig. 1); (2) ibogaine and noribogaine were shown to have affinity for the serotonin transporter [37]; (3) some studies, but not others, reported binding of ibogaine to 5-HT₂ and 5-HT₃ receptors [59]; (4) repeated ibogaine treatment (40 mg/kg, *i.p.*, for 4 days) was observed to increase extracellular serotonin levels in the NAC in an *in vivo* microvoltammetric study [5] and acute treatment with ibogaine (10 mg/kg, *i.v.*) and noribogaine (10 mg/kg, *i.v.*) was observed to increase extracellular serotonin levels in the NAC in an *in vivo* microdialysis study [37]; (5) ibogaine is a hallucinogen at high doses (it is not known yet if noribogaine or 18-MC is also a hallucinogen), and the serotonergic system is well known to be involved in the effects of many hallucinogens; and (6) in animal models, ibogaine induces acute behavioral signs that are very similar to those that have been described as part of the ‘serotonin syndrome’ (e.g., rigidity, tremor, forward posture and forepaw treading) [23]. Noribogaine only produces muscle rigidity. 18-MC also has the indole ring in its structure, but it does not produce any obvious changes in gross behavior; it is not known if it also has affinity for the serotonin transporter.

Therefore, this study was designed to do the following: (1) in order to be able to compare serotonin results to those previously reported with dopamine [36], we assessed acute extracellular changes in serotonin levels in the NAC and striatum (STR) induced by these three drugs in naive rats after *i.p.* administration; and (2) in order to be able to compare results to previous serotonin data reported by others [37], we assessed acute extracellular changes in serotonin levels in the NAC and STR after *i.v.* administration of ibogaine and noribogaine in naive rats. We found that ibogaine, noribogaine and 18-MC have very different effects on serotonin neurotransmission.

2. Materials and methods

2.1. Animal preparation

Female Sprague–Dawley rats, weighting 250–275 g, were used. Under pentobarbital anesthesia, two guide cannulas were implanted stereotaxically in the NAC (coordinates: rostral: +1.6 mm and lateral: ± 0.8 mm from bregma, ventral: –4.6 mm from the skull surface) and the STR (coordinates: rostral: +0.5 mm, lateral: ± 3.0 mm and ventral: –2.0 mm) in opposite sides (left and right) of the brain [44]. The sides were alternated from one rat to the next. The cannulas were fixed firmly to the skull with screws and dental cement. After surgery, dummy probes were inserted and kept in the cannulas until the day of microdialysis. In the *i.v.* administration study, a flexible polyurethane cannula was implanted in the external jugular vein.

2.2. *In vivo* microdialysis

Four or five days after the surgery, while the rat was under brief methohexital anesthesia, dummy probes were replaced by dialysis probes (CMA/microdialysis), 3-mm probes in STR and 2 mm probes in NAC. The rat was placed in a cylindrical cage where it had free access to

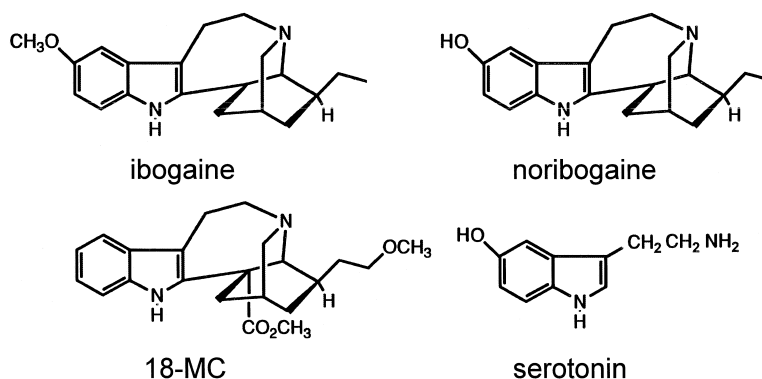


Fig. 1. Structures of ibogaine, noribogaine, 18-MC and serotonin. All compounds contain the indole ring that consists of the benzene ring and attached five-member ring containing nitrogen.

food and water. The probes were perfused continuously with an artificial CSF solution containing (mM) 146 NaCl, 2.7 KCl, 1.2 CaCl_2 , and 1.0 MgCl_2 ; the flow rate was 0.5 $\mu\text{l}/\text{min}$ maintained by a Harvard pump throughout the experiment. Collection of samples (brain perfusate) began the next day. In the i.p. administration study, samples were collected every 20 min for 2 h before and 3 h after drug or saline administration. Ibogaine, noribogaine and 18-MC were administered i.p. at doses of 40 mg/kg. In the i.v. administration study, two i.v. doses of ibogaine or noribogaine, 1 mg/kg and 10 mg/kg, were administered. Samples were collected every 20 min: for 2 h before drug administration, for 1 h after the first dose, and for 2 h after the second dose. Each rat was sacrificed immediately after the experiment, and histological examination of the brain was performed to verify the locations of the probes.

2.3. Drugs

Ibogaine HCl, obtained from Sigma, and noribogaine HCl, provided by NIDA, were dissolved in sterile water. 18-MC, synthesized and provided by M.E. Kuehne, Department of Chemistry, University of Vermont, was dissolved in 0.008 M Na_2HPO_4 solution.

2.4. Serotonin assay

Samples were analyzed by microbore HPLC coupled to an electrochemical detector. The HPLC consisted of an ISCO 100D syringe pump, a 7125 Rheodyne injector, a microbore column (S5 ODS2; 10 cm $\times$ 1 mm i.d., Phenomenex) and a Waters 464 electrochemical detector. The

mobile phase consisted of 6.9 g/l sodium monobasic phosphate, 100 mg/l disodium EDTA, 280 mg/l sodium sulfate, and 150 ml/l methanol; the solution was adjusted with NaOH to pH 5.75 and was pumped at a rate of 0.1 ml/min. A 10- μl sample was injected into the column. The retention time for serotonin was 14.25 min. Chromatograms were processed using Hewlett-Packard HPLC 3D Chem Station software.

2.5. Statistical analysis

The data were expressed as percent (means $\pm$ S.E.) of corresponding basal values. A repeated measures analysis of variance (ANOVA) followed by Neuman–Keuls tests for post-hoc comparisons was used to analyze the data.

3. Results

3.1. Extracellular basal levels of serotonin

In the i.p. administration study, the estimated extracellular serotonin basal values (nM, means $\pm$ S.E.M.) of the four groups of rats were: in the NAC, ibogaine 1.06 ± 0.17 , noribogaine 0.8 ± 0.10 , 18-MC 0.78 ± 0.11 , and saline 0.92 ± 0.13 ; and in the STR, ibogaine 1.05 ± 0.11 , noribogaine 1.03 ± 0.12 , 18-MC 0.95 ± 0.07 , and saline 1.05 ± 0.21 . In the i.v. administration study: in the NAC, ibogaine 1.31 ± 0.24 , and noribogaine 1.21 ± 0.14 ; and in the STR, ibogaine 0.96 ± 0.13 , and noribogaine 1.21 ± 0.21 . These levels, corrected for probe recovery, were based on six baseline samples taken 17–18 h after probe insertion.

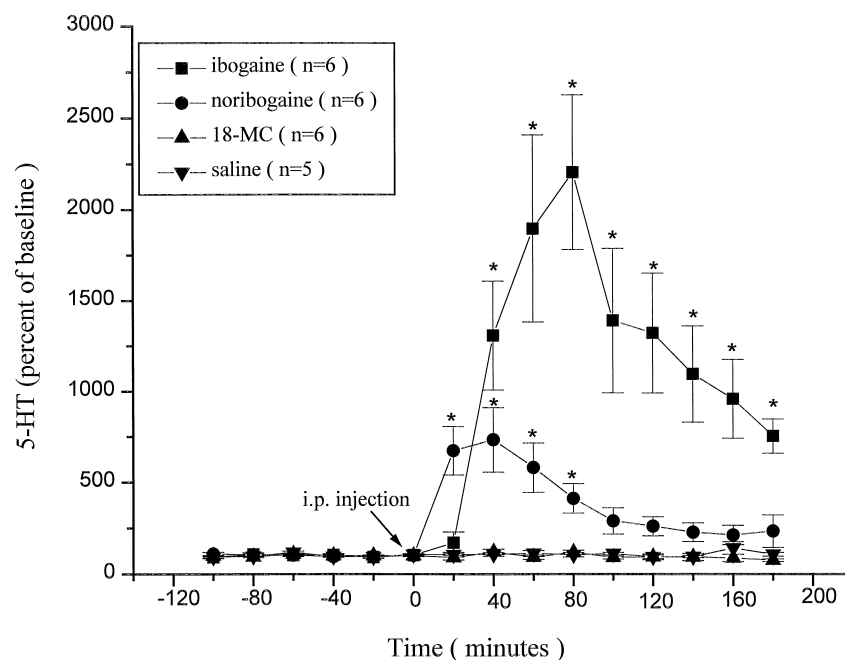


Fig. 2. Changes in extracellular serotonin levels in NAC following administration (40 mg/kg, i.p.) of ibogaine, noribogaine, 18-MC and saline. Data are expressed as percent (means $\pm$ S.E.) of baseline values. * $P < 0.05$, drug vs. saline.

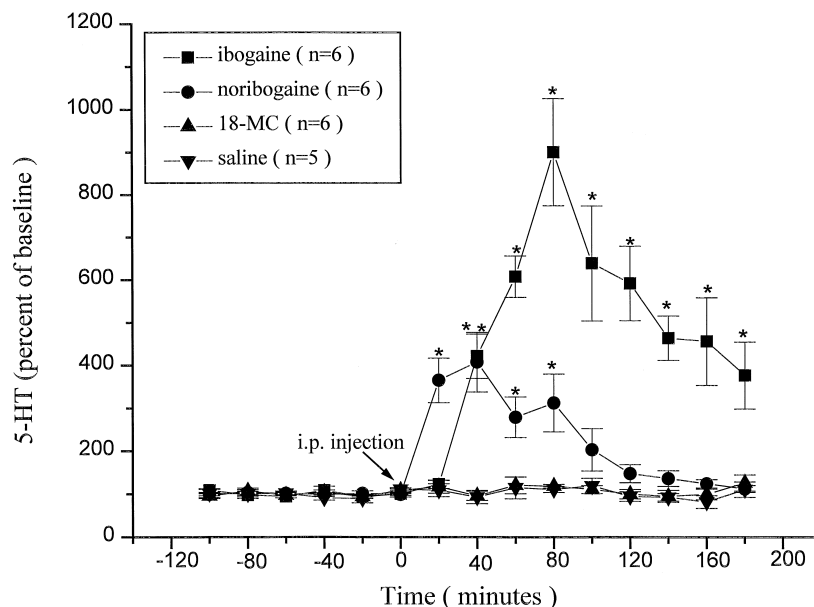


Fig. 3. Changes in extracellular serotonin levels in STR following administration (40 mg/kg, i.p.) of ibogaine, noribogaine, 18-MC and saline. Results are expressed as percent (means $\pm$ S.E.) of baseline values. * $P < 0.05$, drug vs. saline.

There were no significant differences in basal values among drug groups and regions.

3.2. Changes in extracellular serotonin levels in the NAC and STR after i.p. administration

A three-way ANOVA analysis with repeated measures showed that the drugs under study modified the extracellular serotonin levels, and these changes were related to the drugs and the regions studied (drug $\times$ region $\times$ time interaction, $F(24,296) = 2.62$, $P < 0.0001$). Further analysis

showed that in the NAC, as shown in Fig. 2, only ibogaine and noribogaine significantly increased extracellular serotonin levels (compared to saline group, two-way ANOVA, $P < 0.001$ for both drugs). Neuman–Keuls test showed that the significant increases after ibogaine (40 mg/kg, i.p.) began about 20 min after the injection and lasted for at least 3 h ($P < 0.05$ at each time point). The increase reached its highest levels (up to 25-fold) about 60–80 min after the administration, followed by a gradual return to basal levels. In contrast, the significant increases after noribogaine (40 mg/kg, i.p.) (Neuman–Keuls, $P < 0.05$)

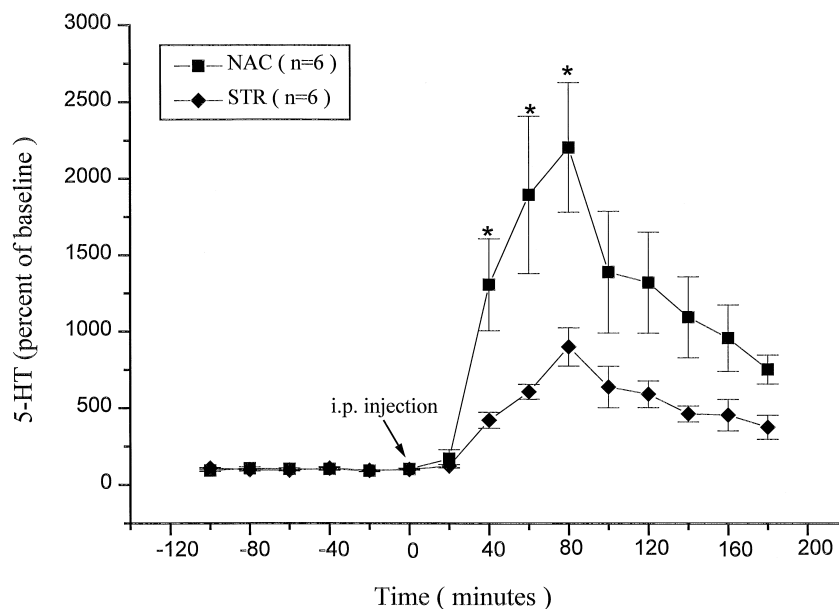


Fig. 4. Comparison of ibogaine (40 mg/kg, i.p.)-induced changes in extracellular serotonin levels in NAC and STR. Data are expressed as percent (means $\pm$ S.E.) of the baseline values. * $P < 0.05$, ibogaine-NAC vs. ibogaine-STR.

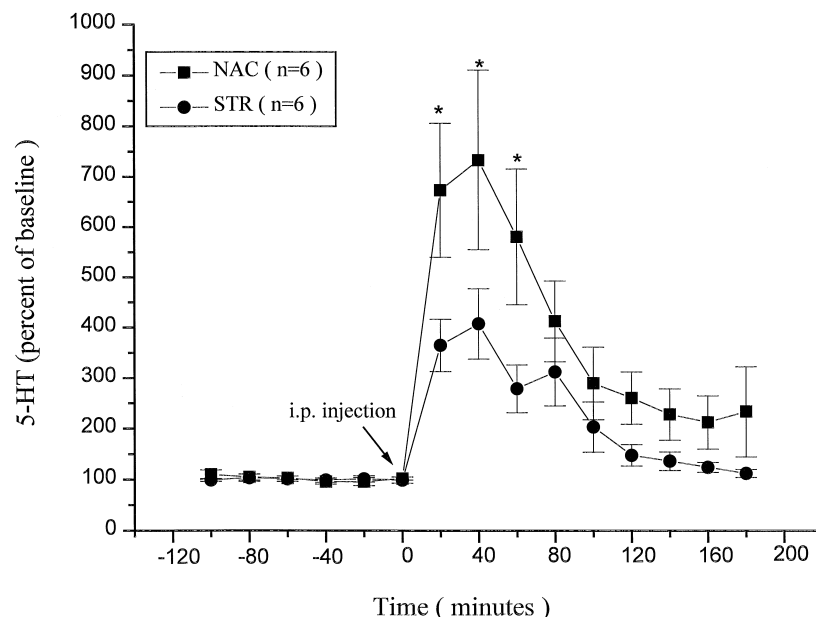


Fig. 5. Comparison of noribogaine (40 mg/kg, i.p.)-induced changes in extracellular serotonin levels in NAC and STR. Data are expressed as percent (means $\pm$ S.E.) of the baseline values. * $P < 0.05$, noribogaine-NAC vs. noribogaine-STR.

began within 20 min, reaching the highest levels (up to 8-fold) about 20–40 min after the injection, and returned to basal levels relatively quickly. 18-MC (40 mg/kg, i.p.) did not produce any significant change in extracellular serotonin levels.

In the STR, as shown in Fig. 3, the changes in extracellular serotonin levels after all drugs were similar to, but less pronounced, than those in the NAC. Only ibogaine and noribogaine significantly increased extracellular serotonin levels (compared to saline group, two-way ANOVA,

$P < 0.001$ for both drugs). The significant increases after ibogaine (40 mg/kg, i.p.) began about 20 min later after the injection and lasted for at least 3 h (Neuman–Keuls, $P < 0.05$ at each time point). But the highest increase was only about 10-fold. The significant increases after noribogaine (40 mg/kg, i.p.) (Neuman–Keuls, $P < 0.05$) began within 20 min, and the highest increase was about 5-fold. Figs. 4 and 5 separately show these regional differences. 18-MC (40 mg/kg, i.p.) did not produce any significant changes in extracellular serotonin levels.

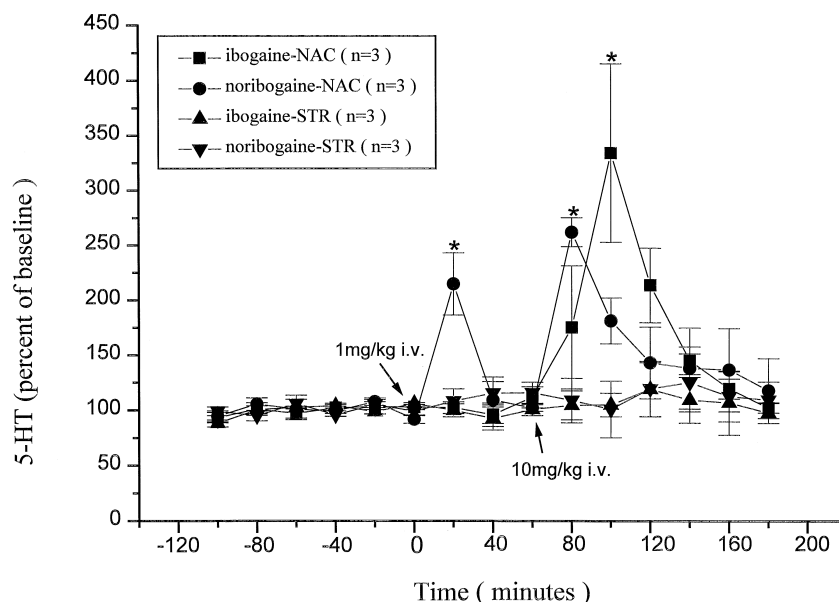


Fig. 6. Changes in extracellular serotonin levels in NAC and STR after i.v. administration of ibogaine or noribogaine. Two doses of ibogaine or noribogaine were injected (i.v.), 1 mg/kg at time zero and 10 mg/kg at 60 min, respectively. Data are expressed as percent (means $\pm$ S.E.) of the baseline values. * $P < 0.05$, drug effect vs. baseline.

In both the NAC and the STR, the ibogaine-induced increases in extracellular serotonin levels were higher and lasted longer (two-way ANOVA, Neuman–Keuls, $P < 0.05$), but peaked about 20 min later, than those induced by noribogaine. The ibogaine-induced increases were greater than the noribogaine-induced increases from 40 min after drug injection until the end of the experiment in the NAC and from 60 min after drug administration until the end of the experiment in the STR.

3.3. Changes in extracellular serotonin levels in the NAC and STR after i.v. administration

Two-way ANOVA analyses showed that both ibogaine (region $\times$ time, $F(8,40) = 2.80$, $P < 0.05$) and noribogaine (region $\times$ time, $F(8,32) = 4.51$, $P < 0.001$) produced significant changes in NAC (drug $\times$ time, $F(8,32) = 3.34$, $P < 0.01$) but not in STR (Fig. 6). Neuman–Keuls tests showed that, at the low dose (1 mg/kg, i.v.), only noribogaine significantly increased extracellular serotonin levels in the NAC ($P < 0.05$); at the high dose (10 mg/kg, i.v.), both ibogaine and noribogaine increased extracellular serotonin levels in the NAC ($P < 0.05$ for both drugs), and the increases induced by ibogaine were higher, but slower in onset, than those induced by noribogaine (at 40 min after 10 mg/kg injection, $P < 0.05$, Neuman–Keuls). Neither ibogaine nor noribogaine induced any significant increases in extracellular serotonin levels at either dose in the STR.

4. Discussion

The results show that ibogaine, noribogaine and 18-MC have different effects on extracellular serotonin levels in the NAC and the STR: ibogaine elicits large increases, noribogaine produces moderate increases, and 18-MC has no effect in either brain region. Therefore, effects on the serotonergic system, at least as reflected in changes in extracellular serotonin levels, may not be involved in the actions of all three of these drugs. This raises a crucial question: do these results mean that the serotonergic system is not important in mediating the anti-addictive property of any of these drugs? The serotonergic system, while not an essential factor in the anti-addictive actions of all three drugs, may still be involved in the anti-addictive actions of ibogaine and noribogaine.

There is an increasing evidence suggesting a role of the serotonergic system in addiction: selective lesioning of the serotonergic innervation in the NAC by local administration of the serotonin neurotoxin 5,7-dihydroxytryptamine increased morphine self-administration [55] and prevented the development of morphine place conditioning [57]. It is well established that cocaine blocks the reuptake of serotonin as well as dopamine and norepinephrine [21]. Clinical studies showed that the serotonergic system may be involved in mediating the euphorogenic and anxiogenic

effects of cocaine [1] and the cue-induced craving for cocaine in addicted patients [52]. Deficient serotonin neurotransmission could be a significant factor in cocaine withdrawal symptoms [43]. The serotonin reuptake inhibitor fluoxetine has been demonstrated to attenuate the discriminative stimulus effects of cocaine in monkeys [56], reduce break-points on a progressive ratio schedule reinforced by cocaine in rats [51] and increase responding to break-point following intracerebral injection of 5,7-dihydroxytryptamine [28]. The effectiveness of specific serotonin reuptake inhibitors, such as fluoxetine, in treating alcohol addicts is under investigation [39]. The serotonin releaser dextfenfluramine was found to reduce heroin self-administration in rats [20].

Serotonin's role in addiction is further supported by compelling evidence for its interaction with the dopaminergic mesolimbic reward system, which originates from the midbrain ventral tegmental area and has projections to the limbic regions, including the NAC. Virtually all abused drugs, directly or indirectly, have a common effect on this reward system, in which dopamine neurotransmission is stimulated [27]. Anatomical evidence indicates that projections from the serotonergic dorsal raphe nuclei innervate both the dopaminergic neurons in the midbrain and their nerve terminals in the striatal and limbic regions [45,62]. Physiological studies show that stimulation of the dorsal raphe nuclei and the consequent increased release of serotonin is associated with a decreased firing rate of dopaminergic neurons and consequently a decreased dopamine release in the STR and possibly other innervated areas [17,26]. 5-HT₂ receptors have been demonstrated to mediate this inhibition [61]. In contrast, inhibition of raphe neurons by 5-HT_{1A} agonists [26], lesions of the dorsal raphe [24], or 5-HT₂ antagonists [8,17,61] have all been shown to disinhibit the dopamine system. Therefore, the serotonergic system could ameliorate reinforcing effects of abused drugs by inhibiting dopamine function.

Other neurotransmitter systems, such as the opioid, glutamatergic and cholinergic systems, have also been shown to interact with the dopaminergic system [63]. For 18-MC, other mechanism(s) probably exist to mediate its anti-addictive action. The decreased dopamine levels induced by all three drugs could result from different mechanisms in different modulating systems. Further studies of 18-MC should provide important information in this regard.

How could ibogaine induce such large increases in extracellular serotonin levels? Although the noribogaine-induced increase can be explained by its inhibition of serotonin reuptake, the marked and prolonged increases induced by ibogaine can only be compared with serotonin releasers, which can increase serotonin levels more than 20-fold [10,18]. We speculate that ibogaine (or an unidentified metabolite) may release serotonin as well as inhibit its reuptake. It may act on serotonergic neuronal cell bodies to stimulate their firing rate and/or directly release

serotonin from the nerve terminals. One drug discrimination study showed that ibogaine was most like the potent serotonin releaser *D*-fenfluramine [53].

What is the role of changes in serotonin levels in the hallucinogenic effect of ibogaine? The serotonergic system has been demonstrated to be involved in the hallucinogenic effect of many drugs, and their interactions with 5-HT₂, especially 5-HT_{2A}, receptors have been shown to be most closely associated with their hallucinogenic effects [9,60]. Some radioligand binding studies, but not others, have reported binding of ibogaine to 5-HT₂ and 5-HT₃ receptors [59]. One behavioral study has also suggested the involvement of 5-HT₂, and possibly 5-HT_{1A}, receptors in ibogaine's actions [42]. Some hallucinogens, such as *p*-chloroamphetamine (PCA), methylenedioxymphetamine (MDA) and methylenedioxymethamphetamine (MDMA), are potent serotonin releasers [3,4,54]. Because of the well-established involvement of the serotonergic system in the hallucinogenic effects of many drugs and the strong effect of ibogaine on this system, we postulate that this system may also mediate ibogaine's hallucinogenic effect. Consistent with this reasoning, we believe that 18-MC is probably not a hallucinogen.

What is the role of changes in serotonin levels in ibogaine's neurotoxic effect? Potent serotonin release has been related to the neurotoxic effects of some serotonin releasing drugs, such as *D*-fenfluramine, PCA and MDMA [3,4,54]. Serotonin reuptake inhibitors were shown to prevent the serotonin release induced by these drugs and attenuate their neurotoxic effects [19]. High levels of serotonin have been suggested to be neurotoxic in some studies, presumably due to some neurotoxic intermediate metabolites of serotonin [25]. It will be interesting to see if serotonin reuptake inhibitors could also attenuate ibogaine's effect on serotonin levels and even prevent its neurotoxic effect. Although both ibogaine and its metabolite noribogaine are also serotonin reuptake inhibitors, binding to different sites of the serotonin transporter may result in different effects on the release of serotonin.

Another interesting observation is that, after *i.p.* administration, the ibogaine-induced increase began more than 20 min after its administration despite the fact that ibogaine reaches the brain within a few min [64]. However, noribogaine induced an increase within 20 min. This difference may imply a role of metabolism in ibogaine's effect on serotonin levels. Noribogaine is the only known metabolite of ibogaine, but even in the *i.v.* administration study, in which 'first pass' metabolism in the liver initially should have been avoided, the ibogaine-induced increase in serotonin levels was still higher, but slower in onset, than that induced by noribogaine after the high dose, providing more evidence of the possible existence of other metabolites.

It is not apparent now why the increases induced by both ibogaine and noribogaine were more pronounced in the NAC than in the STR. However, it has been demon-

strated that, for most abused drugs, the enhancement of extracellular dopamine levels is more pronounced in the NAC than in the STR [11]. The present findings with ibogaine and noribogaine may reflect the critical position of the NAC in the reward system.

In rats, ibogaine induces some acute and characteristic behaviors, including resting tremor, muscle rigidity, forward posture, tail flick and forepaw treading, which are similar to those that have been described as part of the 'serotonin syndrome' [23], which may reflect increased activities of motor neurons in both spinal cord and brainstem. Drugs that can dramatically increase synaptic serotonin levels (e.g., serotonin releasing agents such as fenfluramine and PCA) or directly stimulate serotonin receptors (e.g., 5-HT_{1A} agonists) have all been shown to induce this syndrome [23]. Serotonin reuptake inhibitors alone do not induce this syndrome because of their low efficacy to raise extracellular serotonin levels [10]. The anatomical sites mediating the 'serotonin syndrome' are localized in the lower brainstem and spinal cord, because transecting brain levels as low as posterior to the midbrain raphe nuclei or complete cerebellectomy have no disruptive effects on the syndrome [23]. Serotonin containing varicosities have been observed to make intimate contact with motor neurons and their processes in the brainstem and spinal cord [58], and serotonin can potently potentiate the excitability and responsiveness of motor neurons to incoming excitatory stimuli [22]. 5-HT₂ and 5-HT_{1A} receptors are possibly involved [22]. Therefore, stimulation of the descending pathway of the serotonergic system could also, at least in part, mediate ibogaine-induced behaviors. Noribogaine only produces slight muscle rigidity, and 18-MC has no obvious behavioral effects. The apparent correlation between the effects on the serotonergic system and the gross behavioral effects strongly suggest the involvement of the serotonergic system in the ibogaine-induced behaviors. The immediate appearance of these behaviors and the delayed increase in serotonin levels after both *i.p.* and *i.v.* administration of ibogaine lead us to speculate that ibogaine induces these behaviors by both increasing the synaptic serotonin levels and acting directly on some postsynaptic receptors.

In conclusion, this study shows that the serotonergic system is involved in the acute effects of ibogaine and noribogaine but probably not of 18-MC. This indicates that the serotonergic system may not mediate the anti-addictive action of 18-MC, but it still may mediate the anti-addictive actions of ibogaine and noribogaine. Presumably, multiple mechanisms may underlie the anti-addictive actions of these drugs, but these different mechanisms could result in a similar effect on the mesolimbic reward system. A serotonin releasing activity, by ibogaine or an unknown metabolite, may be involved in ibogaine's actions. The stimulation of the ascending serotonergic pathway may mediate the hallucinogenic effect of ibogaine in humans, which could be analogously reflected, in animals, in the stimulation of the descending serotonergic pathway that

may mediate the acute and characteristic behaviors induced by ibogaine. The data suggest that 18-MC is unlikely to be a hallucinogen. Whether there is a role for serotonin or its receptors in mediating ibogaine's neurotoxic effect is unknown.

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